Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies

To the Editor: We have read with great interest the paper by Praditpornsilpa *et al.*[1] and the related comment by Wish[2] about induction of neutralizing antibodies by biosimilar epoetin products in Thailand. As far as we know, the only Argentine-manufactured epoetin marketed in Thailand is Hemax (Bio Sidus SA, Buenos Aires, Argentina), which is probably the Argentine product mentioned in Praditpornsilpa's report, together with products of other origins. The induction of such antibodies seems to be a class effect of erythropoiesis stimulators and we agree that it is shared by biosimilar and innovator epoetins. This concept emphasizes the importance of a pharmacovigilance plan and risk minimization strategies for epoetin products. However, some statements in both articles can be misleading, including the putative existence of a pure red-cell aplasia (PRCA) epidemic induced by biosimilar epoetins in Thailand and the assumption that no pharmacovigilance is performed for such products.

A point estimation of antibodies and aplasia (as in the report by Praditpornsilpa *et al.*[1]) does not mean/demonstrate the existence of epidemic PRCA induced by biosimilars, as suggested by Wish.[2] Hemax was registered in Argentina in 1990, before the biosimilarity concept arose in Europe, and its formulation has remained unchanged. Pharmacovigilance activities on Hemax include antibodies detection since 1998. Hemax has been in the Thai market since 1997 and, upon requirement of the local licensee, since February 2004 (after the outbreak of PRCA associated to an innovator epoetin product and related to formulation changes), we began to receive sera for anti-epoetin testing from a few patients treated with Hemax that reported loss of efficacy. We suspect that the increased rate of requirements for anti-epoetin antibodies from Thailand reflects the increased interest on PRCA triggered by the epidemics associated to Eprex, in a country in which the rate of aplastic anemia is higher than in Western countries,[3] involving probably human leukocyte antigen background.

The worldwide rate of PRCA associated to Hemax, estimated in 2007 in 1.21 cases per 100,000 treatment-years,[4] seems similar to reports with other epoetins, excluding the already mentioned epidemics induced by Eprex.

A prospective study, including data from all epoetin marketed in Thailand, as the one currently under way by the Thai FDA (together with three Thai scientific societies), should provide a more precise assessment of prevalence and association between PRCA and epoetin products.

1. Praditpornsilpa K, Tiranathanagul K, Kupatawintu P *et al.* Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies. *Kidney Int* 2011; **80**: 88–92.
2. Wish JB. Erythropoiesis-stimulating agents and pure red-cell aplasia: you can't fool Mother Nature. *Kidney Int* 2011; **80**: 11–13.
3. Issaragrisil S. Epidemiology of aplastic anemia in Thailand. *Int J Hematol* 1999; **70**: 137–140.
4. Ferro HH, Donato H, Valtuille R *et al.* Worldwide pharmacovigilance of a biosimilar product containing epoetin (Hemax®). Presented at the 8th Annual Meeting of the International Society of Pharmacovigilance. *Drug Safety* 2008; **31**: 913.

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The Author Replies: Ferro and Gonzalez[1] describe as misleading statements in the article by Praditpornsilpa *et al.*[2] and in the accompanying commentary by this author[3] that there was an epidemic of pure red cell aplasia (PRCA) in Thailand, and that it was caused by the use of biosimilar erythropoiesis-stimulating agents (ESAs). One could dispute that 23 patients with PRCA who were receiving biosimilar ESAs in Thailand constitutes an epidemic based on patient counts, but an incidence rate of 1:2068 is certainly alarming when compared with the virtual absence of ESA-associated PRCA in the United States where biosimilar ESAs are not used. Whether the incidence of PRCA associated with biosimilar ESA use is significantly higher than the background incidence of PRCA in Thailand unassociated with ESA use was not addressed by Praditpornsilpa *et al.*,[2] but this question underscores the importance of tailoring the post-marketing pharmacovigilance program to the specific patient characteristics of each country as the immunogenicity of biosimilars and other therapeutic agents has a genetic predisposition. That said, a high background rate of idiopathic PRCA, an autoimmune disease, in Thailand should be cause for more pharmacovigilance in that country, not less. Irrespective of whether the current state of pharmacovigilance for biosimilar ESAs is currently adequate to assure the safety of patients receiving these agents, this author agrees with Ferro and Gonzalez, Praditpornsilpa *et al.*,[2] and drug regulatory agencies throughout the world that it can be better, especially as increasing numbers of biosimilar agents become available and their market share vs. the reference agent increases because of patent expirations and efforts at cost-containment.

1. Ferro HH, González EB. Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies. *Kidney Int* 2012; **81**: 1273.
2. Praditpornsilpa K, Tiranathanagul K, Kupatawintu P *et al.* Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies. *Kidney Int* 2011; **80**: 88–92.
3. Wish JB. Erythropoiesis-stimulating agents and pure red-cell aplasia: you can't fool Mother Nature. *Kidney Int* 2011; **80**: 11–13.